REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and the following arguments is respectfully requested.

Claims 35-37 are pending and under consideration. Claims 35-37 have been amended as explained below. No new matter has been added as a result of these amendments.

Applicants thank the Examiner for withdrawing the rejection of claims 35-37 under 35 U.S.C. § 112, first paragraph, written description and under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 35-37 Under 35 U.S.C. § 103(a)

Claims 35-37 are rejected under 35 U.S.C. § 103(a), as being unpatentable over O'Rourke *et al.*, U.S. Patent No. 6,165,784 (hereinafter "O'Rourke") and/or Korth *et al.*, *Nature* 6, November 1997, 390:74-77 (hereinafter "Korth") in view of Kuroda *et al.*, *Infection and Immunity*, 1983, 41:154-61 (hereinafter "Kuroda") and/or Manuelidis *et al., Science* 1978, 200:1069-1071 (hereinafter "Manuelidis").

Specifically, the Examiner maintains the rejection in the previous Office Action. The Examiner additionally provides the following comments.

The Examiner states that Applicants' arguments that Kuroda and Manuelidis refer to the TSE causing agent as being a virus instead of a prion are not persuasive. The Examiner alleges that both of these references were published at a time when the prion theory was not generally accepted. Therefore, the Examiner concludes that even if these references erroneously referred to the disease-causing agent as a virus, this does not detract from the important observation made in the references. According to the Examiner, this observation is that animal experiments show that the TSE causing agent is found in B-cells and T-cells of infected animals.

The Examiner further states that O'Rourke and Korth disclose using antibodies as a method of detecting the disease-causing agent. Therefore, the Examiner alleges that it would have been obvious and one would have had a high expectation of success in applying the techniques taught by O'Rourke or Korth to the infected tissue disclosed by Kuroda or Manuelidis in order to improve the sensitivity of the TSE tests by collecting samples containing B-cells and/or T-cells.

Applicants respectfully traverse this rejection for the reasons stated in the previous Amendments. Those arguments are incorporated herein. Important arguments from the previous Amendments are reiterated below. Additional comments are also provided herein.

The present invention is directed to a method of identifying TSE-infected B-cells and T-cells associated with transmissible spongiform encephalopathy (TSE) in a test sample. The prior art teaches that the development of neurological disease after peripheral infection with TSE depends on abnormal prion expansion within the cells of the lymphoreticular system (LRS) (page 19, last paragraph of the specification). Among the immunocompetent and other components of LRS, at least the stem cells, plasma cells, NK cells, B-cells, T-cells, dendritic cells, eosinophiles, basophiles, monocytes, macrophages, reticular cells, capillary sheath cells, polymorphonuclear neutrophiles and mast cells are referred to in the literature. The inventors are the first to determine the roles of different components of the immune system by using a panel of immune-deficient mice inoculated with prions. The inventors found that defects affecting only T-cells had no apparent effect. However, all mutations that disrupted the differentiation and response of B-cells prevented the development of clinical TSE. Additionally, the inventors found that differentiated B-cells are crucial for neuroninvasion by TSE, regardless of the specificity of their receptors. See the paragraph bridging pages 19 and 20 of the specification.

Investigations performed specifically by the inventors demonstrate that $CD8^+$ cytotoxic and $CD4^+$ helper T-cells are not rate limiting for TSE after peripheral inoculation of prions (specification, paragraph bridging pages 21 and

22). Further studies suggest that B-cells transport prions from lymphoid organs to nervous tissue (page 23, first full paragraph and Table 2 on page 26).

Thus, the inventors identified B-cells and B-cells dependent processes as a limiting factor in the development of TSE after peripheral infection and that the TSE-infected B-cells are the bottle neck of disease promulgation (page 27, first paragraph).

On pages 27-29, the specification discloses that the inventors demonstrated in their studies that although T-cells were not able to directly propagate infectivity, B-cells interact with T-cells via a secondary infection.

Through these findings, an assay according to the present invention is provided which contemplates the monitoring of biological or biochemical parameters of B-cells and T-cells to determine the occurrence of secondary infection as an indicator of the disease progress (page 30, first two paragraphs).

As noted above, the LRS contains many different type of cells. There is literature in the art that has come to incorrect conclusions, opposite to Applicants'. See the middle of page 32 of the specification. For example, Lasmezas (*J. of Virology*, 70:1292-1295 1996)) and O'Rourke (*J. of General Virology*, 75:1511-1514 (1994)) concluded in two independent investigations that the primary route of infection involved dendritic cells in the LRS while the secondary route of infection appeared to be a direct neural spread from the peritoneum. Thus, the conclusions of Lasmezas and O'Rouke teach away from the findings of the inventors as to the actual infection route.

Other independent studies such as those of Bueler (*Nature*, 356:577-582 (1992)) and Blattler (*Nature*, 389:69-73 (1997)) are also discussed in the instant specification (page 33). Bueler and Blattler do not provide any insights as to the role of B-cells and T-cells in TSE, or any other specific cells within the LRS.

Applicants have provided an ample number of examples in the specification to support the above conclusions. An example is apparent from Figure 10, showing that purification of B-cells prior to carrying out a Western blot with mab6H4 leads to enrichment of PrP^{Sc}. Another example is the investigations conducted by the inventors using a buffy coat that is totally purified

from B-cell and/or B-cell debris which do not transmit TSE. See page 46 for example. Figure 10 also shows the results of T-cells purification as discussed on pages 52-53 of the specification.

Applicants' arguments in the previous Amendments are incorporated herein. Applicants previously argued that the cited prior art incorrectly teaches the transmission of TSE via a virus instead of a prion. Furthermore, Applicants argued that the Examiner's motivation to combine the teachings of the prior art employs the improper standard of "Obvious to Try".

While Applicants respectfully disagree with the Examiner's position, in an effort to expedite prosecution of the instant application, claims 35-37 have been amended in order to point out the features of the present invention as discussed above.

Specifically, claims 35-37 have been amended to recite "obtaining a test sample that is suspected of TSE infection". Claims 35 and 37 have been amended to recite "wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection" and "identifying TSE-infected B-cells based on the presence of said signal". Claims 36 and 37 have been amended to recite "identifying TSE-infected T-cells based on the presence of said signal" and "wherein the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection".

Support for these amendments can be found on page 22, lines 2-6, page 27, lines 1-9, page 29, first full paragraph, page 30, lines 3-5 and throughout the specification as described above. Specifically, on page 27, lines 1-9, the specification discloses that "the inventors have identified B-cells and B-cells dependent processes as a limiting factor in the development of transmissible spongiform encephalopathy after peripheral infection" and "B-cells are the bottle neck of disease promulgation". Therefore, B-cells are identified as being associated with TSE promulgation and primary infection. On page 22, lines 2-6, the specification discloses that "T-cells are not rate-limiting for spongiform encephalopathy after peripheral inoculation of prions". Therefore, T-cells are identified as being associated with TSE promulgation and secondary infection.

On page 29, in the first full paragraph, the specification states that "[s]pleen mice contains both T-cells and B-cells, and upon infection of the B-cells, a B-cell mediated secondary infection of spleen mice's T-cells takes place (see e.g. Table 6)". Furthermore, on page 30, lines 3-5, the specification states that "Indeed, the present invention allows the distinction between the occurrence of tse-infected B-cells alone and the further occurrence of secondary tse-infected T-cells". In other words, after infection of the B-cells, infection of the T-cells takes place. Thus, B-cells are identified as being associated with TSE promulgation and primary infection while T-cells are identified as being associated with TSE promulgation and secondary infection.

As recognized by the Examiner, Kuroda and Manuelidis disclose the mode of transmission of TSE via a viral infection instead of a prion infection. While Kudora and Manuelidis test B-cells and T-cells in their studies, neither one discloses or suggests that B-cells and T-cells should be tested exclusively for TSE. Applicants wish to point out to the Examiner, that based on the theory of a virus as the TSE causing agent, many different types of cells can be postulated as a carrier for the disease. In fact, Kuroda discloses on page 156, second paragraph that macrophages are infected. Kuroda appears to suggest that macrophages can promulgate and propagate TSE infection. Manuelidis discloses on page 1071, last paragraph, that infection is via the hematogenous system. Thus, Manuelidis appears to suggest that many other type of cells can promulgate or propagate TSE infection. Therefore, similar to Lasmezas and O'Rouke as discussed above, Kuroda and Manuelidis teach away from the present invention.

Thus, Kuroda and Manuelidis do not explicitly or implicitly teach testing of B-cells and T-cells exclusively for TSE. Kuroda and Manuelidis do not explicitly or implicitly teach testing of B-cells and T-cells for TSE-indication of primary and secondary infection, respectively.

As recognized by the Examiner, while O'Rouke and Korth disclose that prions are infectious agents causing TSE, O'Rouke and Korth do not disclose or suggest testing B-cells or T-cells in order to identify TSE. As mentioned above, it

has been suspected in the art that cells of the LRS might transmit TSE via prions. Also as mentioned above, the LRS has many different type of cells. However, the prior art does not disclose or suggest that B-cells and T-cells specifically and exclusively transmit TSE via prions. Furthermore, the prior art does not disclose or suggest that infected B-cells and T-cells are indications of primary and secondary propagation of TSE infection, respectively. Thus, O'Rouke and Korth do not remedy the deficiencies of Kuroda and Manuelidis.

Finally, Applicants respectfully submit that since Kuroda and Manuelidis teach away from the presently claimed invention, it is improper to combine their teachings with the teachings of O'Rouke or Korth.

For all of the above reasons, Applicants respectfully request withdrawal of the rejection of claims 35-37 under 35 U.S.C. § 103(a).

Claims 35-37 have been additionally amended to correct typographical errors. Specifically, the claims now recite "T-cells" and "B-cells" instead of "B cell" or "T cell".

While Applicants respectfully disagree with the Examiner's prior art rejection, Applicants have amended the claims in order to distinguish the presently claimed invention from the disclosures and teachings of the cited prior art. If amendments to the claims can be suggested in order to pass the claims to allowance, the Examiner's assistance is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Section 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, he/she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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